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TOPIC PAPER

Basic mechanisms of urgency: roles and benefits of pharmacotherapy

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Abstract
Introduction Since urgency is key to the overactive bladder syndrome, we have reviewed the mechanisms underlying how bladder filling and urgency are sensed, what causes urgency and how this relates to medical therapy.
Materials and methods Review of published literature.
Results As urgency can only be assessed in cognitively intact humans, mechanistic studies of urgency often rely on proxy or surrogate parameters, such as detrusor overactivity, but these may not necessarily be reliable. There is an increasing evidence base to suggest that the sensation of 'urgency' differs from the normal physiological urge to void upon bladder filling. While the relative roles of alterations in afferent processes, central nervous processing, efferent mechanisms and in intrinsic bladder smooth muscle function remain unclear, and not necessarily mutually exclusive, several lines of evidence support an important role for the latter.
Conclusions A better understanding of urgency and its causes may help to develop more effective treatments for voiding dysfunction.

Keywords Urgency · Urge to void · Bladder sensation

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Introduction

Urgency is the key symptom of the overactive bladder syndrome (OAB) and is defined as 'the complaint of a sudden compelling desire to pass urine, which is difficult to defer' [1]. A better understanding of the genesis of urgency and its relationship to other aspects of bladder function is required to unravel the pathophysiology of OAB and to develop more effective treatments. An extended version of the thoughts discussed in this manuscript has been published elsewhere [2].

Implications of the use of surrogate parameters for urgency

The definition of urgency as a desire implies that it can only be measured in cognitively intact human beings. As a sensation it can be affected by neurological disorders and may, therefore, be perceived differently in patients with neurological lesions. Patient-activated keypad devices [3] or an 'urgeometer' [4] have been proposed as tools to capture the sensation of urgency in an objective fashion, but until now they have not been widely used. By contrast, mechanistic studies on urgency have employed the use of isolated tissues and experimental animals. As neither allows assessing a desire, they rely on surrogate markers such as non-voiding detrusor contractions (NVDCs). Several studies have explored the relationship between urgency and detrusor overactivity (DO). Only about half of all patients with DO experience urgency [5], whereas among patients with urgency 44–69% exhibit DO during pressure-flow studies [6–9]. The correlation of urgency with DO is higher in males than in females, and in incontinent compared with continent patients. Possibly

urgency in the absence of DO is not a separate entity, but rather part of a spectrum of bladder dysfunction [10]. Finally, abnormal filling sensations can be reported during fake cystometry [11]. Despite these limitations, NVDCs remain the most frequently used surrogate parameter to study mechanisms related to urgency in experimental animals. Other studies have linked specific mechanisms to the frequency of detrusor contractions or the number of incontinence episodes, rather than the occurrence of urgency. However, not all detrusor contractions are well captured by standard pressure-flow studies.

Two other factors are pivotal to the understanding of urgency. Firstly, as urgency is always a pathological sensation, it does not necessarily involve the same mechanisms as those occurring in response to physiological bladder filling. This limits the extrapolation from findings in animals or healthy individuals to those with urgency. Secondly, the ease with which the term urgency is used in English belies the lack of clarity relating to this distinction from normality in most other languages. The implications of all of these issues need to be considered in the interpretation of the subsequently presented data.

Differential sensing of bladder filling and urgency

Physiological filling signals from the bladder are conveyed to the spinal cord by the pelvic, hypogastric and pudendal nerves. They comprise thin, but myelinated, Aδ-fibres and even thinner and non-myelinated C-fibres, the latter exhibiting slower conductance [12]. The Aδ-fibre endings are located in the detrusor smooth muscle layer and are the most sensitive nerve endings in the bladder; accordingly, they are referred to as 'tension receptors' and are considered to be the primary mediators of the physiological sensation of bladder fullness. On the other hand, the nerve endings of the C-fibres are found in the urothelium and lamina propria [13]. The C-fibres are thought to be only activated by distension that is greater than that required to activate Aδ-fibres and are considered to be less sensitive to contraction than to bladder distension. Factors which are considered to be important in pathology including high osmolality, high ambient KCl concentration or inflammation can activate a subgroup of C-fibres. From these data it can be concluded that C-fibres may primarily be involved in pathological situations and apparently are less important in the sensation of physiological bladder filling (except close to functional bladder capacity); these properties makes them a better candidate to be involved in the sensation of urgency. The non-neuronal release of neurotransmitters may also have a direct stimulatory effect on C-fibres [14, 15]. As they originate largely from the urothelium [16], the urothelium may play a specific role in generating urgency.

Several lines of evidence support the concept that urgency is a pathological sensation which is sensed by mechanisms which are at least partly distinct from those involved in sensing bladder filling. For example, some investigators have explored urgency by determining where the sensation is felt. In one study patients with painful bladder syndrome (PBS), OAB, stress urinary incontinence (SUI) and asymptomatic controls were asked to indicate the location of their urinary urge/urgency/discomfort on a body map [17]. Controls and SUI patients localised the urge to void to the suprapubic region only, whereas more than half of patients with PBS and a minority of those with OAB pointed to both suprapubic and vulval/urethral locations as the source of their urinary urgency/discomfort.

Functional position emission tomography studies have identified areas within the brain which are activated during storage and voiding, and these areas are underperfused in patients with DO [18]. Similar studies have identified that different areas of the cortex may be active during the perception of the physiological sensation of urge as compared to urgency [19] and there may be significant differences between those with 'good' as compared to 'bad' bladder control [20]. Some drugs such as opioid receptor agonists, gabapentin or GABA receptor ligands [21] and also muscarinic antagonists with good penetration into the brain such as oxybutynin [22] may exert beneficial effects on urgency by interfering with these central processing mechanisms.

What causes non-voiding detrusor contractions and urgency?

Non-voiding detrusor contractions could result from multiple causes. These include alterations at the level of the sensory signals originating in the afferent bladder nerves ('sensory urgency'). Equally possible are alterations at the level of the efferent nerve signals to the detrusor ('motor urgency'). Finally, an intrinsic malfunction of the smooth muscle is also possible (myogenic theory). Of note, these three possibilities are not necessarily mutually exclusive. The currently available evidence is insufficient to fully support one of these theories to the exclusion of any of the others and indeed it is likely that a different admixture of pathophysiology is present in different patients. In the following we will largely focus on the myogenic theory as this has been investigated in more detail than the other options and is also supported by circumstantial evidence from pressure-flow studies [23, 24].

Detrusor smooth muscle contractions can occur spontaneously or be evoked by paracrine factors and/or neurotransmitters. Physiological voiding appears largely driven by neurotransmitter-induced detrusor contractions. Human physiological bladder contractions are evoked by the

neurotransmitter acetylcholine acting on muscarinic receptors, largely the M_3 receptor [25]. Their coupling to contraction involves voltage-operated Ca^{++} channels and rho kinase [26]. Paracrine mediators of detrusor contraction include non-neuronal acetylcholine [14] and ATP [27], the latter acting via ligand-gated ion channels. The relative contribution of non-neuronal stimuli, is physiologically low in humans as compared with other species [28] but can increase under pathological conditions [27, 29]. Alterations of cellular Ca^{++} handling [30] and of rho kinase [31] may occur in disease and can contribute to alterations of muscle contractility by neuronal and paracrine agents. Spontaneous contractions play a smaller role in humans than in rodents, and it is not fully clear whether they are involved in the physiological resting tone of the bladder and/or DO, and/or are an epiphenomenon of in vitro conditions [32]. Micromotions may be an in vivo correlate of spontaneous contraction [33] and are more frequent in patients with sensory urgency [34].

Some pathologies leading to bladder dysfunction including DO and urgency may be associated with structural alterations of the bladder which can persist even after the causative insult is removed. For example, mural changes occur in the bladder wall associated with both ageing and bladder outlet obstruction (BOO), which include loss of detrusor muscle volume, decreased neuronal density, increased intramuscular fibrosis and increased excitability of detrusor muscle [35]. Moreover, BOO can be associated with repeated episodes of prolonged detrusor ischemia [36]. Some of these alterations as well as DO and urgency can persist after removal of obstruction both in animals [37] and patients [38].

How do drugs affect non-voiding detrusor contractions and urgency?

The current medical treatment of OAB largely rests on the use of muscarinic receptor antagonists [39, 40]. While the best way to assess urgency in OAB patients is still under debate [41, 42], several studies, largely based on counting urgency episodes, have demonstrated reductions of urgency using several muscarinic receptor antagonists including darifenacin [43, 44], fesoterodine [45–47], propiverine [48], solifenacin [48–52], tolterodine [46, 50, 53, 54] and trospium [55]. For some drugs beneficial effects on urgency have also been demonstrated using other means of assessment including several rating scales [44, 55–61]. Interestingly, several studies indicate that muscarinic receptor antagonist will reduce urgency episodes also in continent patients [62], indicating that they may genuinely have an action on urgency itself and not only produce a response that is secondary to reducing the number of incontinence episodes. However, it should not be ignored that such drugs did not significantly affect urgency in all studies [57, 63, 64]. Taken together these data demonstrate that muscarinic receptor antagonists as a class reduce the number of urgency episodes as well as urgency severity in OAB patients irrespective of the presence of incontinence and without major effects on physiological voiding.

Potential novel treatment of urgency, DO and/or OAB such as β_3-adrenoceptor agonists [65], vanilloids [66], botulinum toxin [67] as well as agents acting on the central nervous system [68], apparently make use of all of the above-mentioned mechanisms but their specific effects on urgency largely remain to be established, particularly in direct comparison with muscarinic receptor antagonists.

Conclusions

Urgency is a pathological sensation which differs at least partly from the physiological urge to void upon bladder filling. Mechanisms involved in urgency are not necessarily the same as those involved in DO or in other OAB symptoms such as frequency, nocturia and urgency incontinence. Specifically, uncertainty concerning the validity of DO as a surrogate marker of urgency is a stumbling block for further research in this area. While muscarinic receptor antagonists have some efficacy against urgency, a better understanding of the underlying pathophysiology is likely to help the development of more effective treatments for this bothersome symptom.

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